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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,663	08/31/2005	Shizuo Akira	31671-211618	1905
26694	7590	06/05/2007		
VENABLE LLP P.O. BOX 34385 WASHINGTON, DC 20043-9998			EXAMINER BERTOGGIO, VALARIE E	
			ART UNIT	PAPER NUMBER
			1632	
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			06/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/517,663

Applicant(s)

AKIRA, SHIZUO

Examiner

Valarie Bertoglio

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 24 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 20,22 and 24-26 is/are pending in the application.  
4a) Of the above claim(s) 10-16 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 20 is/are allowed.
- 6) ☒ Claim(s) 22,24-26 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 13 December 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/20/2007 has been entered.

Claim 20 is directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(b), claims 22, and 24-26 are directed to the process of making or using the allowable product, previously withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104. Claims 10-16, directed to the invention(s) of Inventions II and IV set forth in the restriction requirement dated 04/04/2006 do not require all the limitations of an allowable product claim, and have NOT been rejoined.

Because a claimed invention previously withdrawn from consideration under 37 CFR 1.142 has been rejoined, **the restriction requirement between groups I and III as set forth in the Office action mailed on 04/04/2006 is hereby withdrawn.** In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Claims 1-9, 17-19 and 23 are cancelled. Claims 10-16 are withdrawn. Claims 10-16, 20, 22 and 24-26 are pending. Claims 20, 22 and 24-26 are under consideration in the instant office action.

*Claim Objections*

The objection to claim 20 is withdrawn in light of Applicant's amendment of the claim.

*Claim Rejections - 35 USC § 112-1<sup>st</sup> paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

*Enablement*

Claims 22 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method of screening substances that promote or suppress a response to triacylated mycobacterial lipoproteins comprising contacting peritoneal macrophages isolated from the transgenic TLR-1 inactivated mouse of claim 20, which exhibits a decreased responsiveness to triacylated mycobacterial lipoproteins, with a substance, contacting peritoneal macrophages isolated from a wild-type littermate control mouse with said substance, and comparing the response between the TLR-1 inactivated peritoneal macrophages and the control macrophages wherein an increase in said responsiveness in comparison to the control is indicative of a substance that promotes a response to a mycobacterial lipoprotein/lipoprotein in a TLR-1 independent manner and wherein a greater decrease in responsiveness to a mycobacterial lipoprotein/lipopeptide in comparison to a wild-type control mouse is indicative of a substance that inhibits a response to a mycobacterial lipoprotein/lipoprotein in a TLR-1 independent manner, does not reasonably provide enablement for use of the claimed method using any cells of the mouse of claims 20, screening for substances that modulate responsiveness to any mycobacterial lipoprotein/lipopeptide other than triacylated mycobacterial proteins, or screening for

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modulators of responsiveness to triacylated mycobacterial lipoproteins that act through TLR-1 using the indicators as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are directed to a method of screening modulators of macrophage response to mycobacterial lipoproteins/lipopeptides. The claims are broad in 3 respects. First, the claims encompass use of any cells isolated from the TLR-1 deficient mouse of the invention. Second, the claims encompass defining modulators of any mycobacterial lipoprotein, including diacylated lipoproteins as opposed to just triacylated mycobacterial lipoproteins that are recognized by the subject TLR-1 protein. Finally, the claims are broad, and perhaps scientifically unsound, in the controls and indicators recited and set forth in the specification.

Generally, the specification discloses: production of a TLR1 knockout mouse and production of a TLR2 knockout mouse (pages 19-20); preparation of thioglycollate-stimulated peritoneal macrophages from wild type mice, TLR1 knockout mice and TLR2 knockout mice (page 21); a response (i.e. production of the inflammatory cytokines TNF $\alpha$  and IL-6) from macrophages of wild type mice when said macrophages are exposed to the 19-kD lipoprotein from *Mycobacterium tuberculosis* while macrophages from TLR1 knockout mice exhibited a blunted response (i.e. comparatively less production of TNF $\alpha$ ) when treated as such (pages 21-22); blunted response from macrophages of TLR1 knockout mice when said macrophages are exposed to the synthetic triacylated peptide Pam<sub>3</sub>CSK<sub>4</sub> (page 23); and blunted response from macrophages of TLR1 knockout mice when said macrophages are exposed to several synthetic triacylated synthetic peptides including Myr<sub>3</sub>CSK<sub>4</sub>, Lau<sub>3</sub>CSK<sub>4</sub>, N-Pam-S-Lau<sub>2</sub>CSK<sub>4</sub> (i.e. N-palmitoyl-S-dilaurylglycerol) and JBT3002 (pages 24-26).

The peritoneal macrophages were isolated from the mice and were assayed in vitro by for a response to various bacterial lipoproteins. No other cell type was assayed. The specification also specifies that TLR-1 is responsive to tri-acylated lipoproteins, but not diacylated lipoproteins (page 23, lines 8-11 and paragraph bridging pages 25-26).

Thus, absent evidence that TLR-1 is active in any cell type other than peritoneal macrophages, the claimed method is not enabled for use of any cell type other than peritoneal macrophages. Furthermore, because the specification has established that diacylated lipoproteins are not recognized by TLR-1, the claims are only enabled for screening for modulators of responsiveness to tri-acylated mycobacterial lipoproteins.

With respect to the controls used in the claimed method, the specification teaches at page 7, line 7 and at page 17, that the controls are peritoneal macrophages isolated from wildtype littermate mice. The claims recite that an increase in responsiveness to the lipoprotein compared to a control is indicative of a substance that promotes a response to a mycobacterial lipoprotein. If a response is increased to a greater

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degree in the TLR-1 deficient cells than in the wildtype cells, then the response cannot be acting through TLR-1, since it is deficient in the TLR-deficient cells. Thus, the response must be the result of a TLR-1 independent mechanism. Such a mechanism would also be present in the wild-type cells and would only be detectable in the TLR-1 deficient cells over the wildtype cells if the wild-type cell response was already at a maximal level or if the indicator were a greater increase in response in the TLR-1 deficient cells in comparison to the wildtype cells. The claim reads "An increase in responsiveness in comparison to a control", which is interpreted to mean a greater increase in the TLR-1 deficient cells as compared to any increase in response that may occur in the control cells.

With respect to screening for suppressors of the lipoprotein response, the claim recites that a decrease in responsiveness to said mycobacterial lipoprotein compared to a control (defined above as a wildtype macrophage cell) is indicative of a substance that suppresses a response. The response in TLR1 deficient cells is already suppressed in comparison to wildtype cells. Because TLR1 is deficient, a further decrease in responsiveness these cells would indicate a suppressor of the response that acts through a TLR-1 independent mechanism. Furthermore, it is noted that any decreased responsiveness observed in the TLR1 deficient cells should also be observed in the wildtype cells. Because the response is already decreased in the TLR-1 deficient cells compared to wildtype control cells, the indicator, as worded in the claim, would not work. It appears a more appropriate indicator would be wherein a decreased responsiveness is observed in the wildtype cells in comparison to the TLR1 deficient cells.

It is noted that appropriate controls for the claimed method would also include TLR-1 deficient macrophages that are not treated with the substance to be screened.

***Claim Rejections - 35 USC § 112-2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of Applicant's amendment to the claim.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3) The rejection of claims 1-7 under 35 U.S.C. 102(a) as being anticipated by Henneke et al (Journal of Immunology, 167:7069-7076, 12/15/2001) is withdrawn.

The declaration under 37 CFR 1.132 filed 02/20/2007 is sufficient to overcome the rejection of claims 1-7 based upon anticipation under 35 USC 102(a) by Henneke et al (Journal of Immunology, 167:7069-7076, 12/15/2001).



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*Conclusions*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. There is a number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Valarie Bertoglio', with a long horizontal flourish extending to the right.

Valarie Bertoglio  
Primary Examiner  
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